Surgical Neurology International

SNI: Neuro-Oncology, a supplement to Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: Daniel Silbergeld, University of Washington Medical Center, Seattle, Washington, USA

Treatment of Gliomas: How did we get here?

Michelle M. Chowdhary, Chibawanye I. Ene, Daniel L. Silbergeld

Department of Neurological Surgery, University of Washington, Seattle, Washington, USA

E-mail: Michelle M. Chowdhary - michelle.cecchini@gmail.com; Chibawanye I. Ene - chiba@uw.edu; *Daniel L. Silbergeld - dls@u.washington.edu
*Corresponding author

Received: 15 October 14 Accepted: 15 October 14 Published: 13 February 15

This article may be cited as:
Chowdhary MM, Ene CI, Silbergeld DL. Treatment of Gliomas: How did we get here?. Surg Neurol Int 2015;6:S85-8.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2015/6/2/85/151348

Abstract

Over the past 30 years, the treatment of gliomas has become more multi-modality with clinical trials demonstrating that adjuvant chemo-radiation following surgery improves survival of patients. Unfortunately, this advance in therapeutic intervention has had a modest impact on patient survival, with only a 3–6 month improvement in survival during this time period. In this review, we discuss the progress made in each key aspect of glioma treatment; chemotherapy, surgery and radiation therapy. We present key clinical trials that were used as basis for current management guidelines for patients with gliomas. Ultimately, it is clear that future treatments of patients with gliomas will entail specific chronologic combinations of these three modalities in personalized regimens designed for individual patient tumor sub-type.

Key Words: Chemotherapy, gliomas, multi-modality, radiotherapy, surgery

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.151348

Quick Response Code:

INTRODUCTION

The three modalities currently in use for treating gliomas (chemotherapy, surgery, radiation) have been used for treating cancer for decades. Over the past few decades, it has become apparent that specific combinations of these modalities are necessary to curb progression of disease. Historically, clinical trials have focused on assessing the impact of single agents or specific modalities with modest impact on survival. With more sophisticated clinical trials, it is clear that multi-modality is the key to slowing disease progression.

In this review, we discuss sentinel clinical trials and studies that guide our current multi-modality management of patients with gliomas.

CHEMOTHERAPY

The beginning of chemotherapy use in gliomas was in the 1970s with the first trials of carmustine (BCNU). The Brain Tumor Study Group (BTSG) published a clinical trial of 222 patients receiving BCNU alone, radiation therapy (RT) alone, BCNU + RT, or supportive care. The patients who received BCNU +RT and RT alone survived the longest, but the combination therapy had a higher percentage of survivors at 18 months than RT alone.[22] This finding was confirmed in a later study by the BTSG, which included semustine (CCNU) and BCNU.[23] Since these first trials of nitrosoureas with gliomas, there have been many trials comparing BCNU + RT to RT and multiple other agents, including procarbazine, dacarbazine, and dibromodulcitol. These trials all showed no difference between the agents in terms of survival.[1,15]

In the 1990s, procarbazine–CCNU–vincristine (PCV) was compared with BCNU in a randomized controlled trial (RCT) involving 133 patients. The PCV arm showed improved survival and increased time to progression compared with BCNU arm, though this effect was only seen in the anaplastic astrocytoma (AA) patients and not in the glioblastoma multiforme (GBM) patients.[8] A later RCT

showed that RT with PCV showed no survival advantage over RT alone for patients with malignant gliomas.[13]

Most trials of RT alone versus RT with nitrosoureas show either no survival benefit or only a statistically significant benefit at 18 months. Due to the generally small numbers of patients in these trials, Fine *et al*.[2] performed a meta-analysis of data from these trials in 1993 showing that there is a 10.1% increase in survival at 1 year for RT plus chemotherapy. This effect is greater in the AA patients. The efficacy of Nitrosorueas have also been assessed following delivery via different routes, with intra-arterially delivery demonstrating worse outcomes than intravenous administration.[15]

In 1999, the O6-methylguanine DNA methyltransferase inhibitor, Temozolomide (TMZ) was granted FDA approval for use in recurrent GBM and then approval for primary GBM in 2005. It is now standard of care chemotherapy for newly diagnosed malignant gliomas. Stupp *et al*.[19] published an RCT comparing RT alone to RT plus adjuvant TMZ. A total of 573 patients with malignant glioma were randomized and the relative risk of death for patients in the TMZ arm was decreased by 37%. Two-year survival rate in the RT+ TMZ group was 26.5% compared with 10.4% in the RT alone group. Compared with previous chemotherapy regimens, TMZ is better tolerated with the main side effect being myelosuppresion in less than 10% of patients. Therefore, till date, it appears to be the most efficacious alkylating agent for GBM.

Angiogenesis inhibitors have had many recent studies showing effectiveness in recurrent GBM. In 2009, Bevacizumab was FDA approved for use in recurrent GBM patients. The first phase II study by Vredenburgh *et al*.[21] showed that bevacizumab and irinotecan given to patients with recurrent malignant gliomas, showed a 6-month progression-free survival (PFS) of 38%, 30% for those patients with GBM. The radiographic response rate was 1 patient with complete response and 19 patients with partial response (>50% decrease in tumor cross section). Bevacizumab has also been studied as mono-therapy in recurrent GBM demonstrating minimal toxicity albeit lower PFS.[3] The use of bevacizumab in newly diagnosed GBM was studied by adding bevacizumab to the standard therapy of TMZ + RT. This study looked at 637 patients randomized to bevacizumab plus standard therapy or placebo plus standard therapy. The overall survival (OS) was the same between the two arms (15.7 versus 16.1 months) while the PFS was slightly longer in the bevacizumab group (although it did not reach statistical significance).[4]

Others have attempted local delivery of chemotherapeutic agents within tumor bed following surgical resection. One example is the use of BCNU wafers (Gliadel) in recurrent glioma where a double-blinded, randomized prospective trial showing a 6-month OS of 64% in BCNU wafer implanted patients compared with 44% in placebo treated patients. Studies with concomitant use of TMZ with BCNU wafers show efficacy as well.[10] This suggests that one of the factors impeding efficacy of chemotherapeutic agents may be their inability to reach the target within the brain. It also shows that local delivery of chemotherapeutic agents via safe mechanisms that do not target normal brain cells could be part of the future for treating this devastating disease.

SURGERY

First line therapy of newly diagnosed gliomas is biopsy or maximal surgical excision for establishment of diagnostic tissue. The benefits of surgical resection for both high- and low-grade gliomas have been debated. Studies in the past two decades have shown support for maximal resection of malignant glioma giving survival benefit to patients if worsening neurologic deficits can be avoided. An early retrospective study by Simpson *et al*.[17] looked at 645 patients in the radiation therapy oncology group (RTOG) database and compared the OS of patients with complete resection or partial resection and biopsy only. The median survival for complete resection was 11.3 months, partial resection 10.4 months, and 6.6 months for biopsy only. Other factors that gave survival benefit were age <40, Karnofsky performance score (KPS)>70, and frontal lobe location.

A prospective RCT looked at BCNU wafer implantation using computed tomography (CT) and magnetic resonance imaging (MRI) data to determine extent of resection with complete resection >90% tumor volume. Both placebo and BCNU wafer groups saw a survival advantage when complete resection was done.[24]

Recently, 5-aminolevulinic acid (5-ALA) has been studied as an adjunct to tumor resection of gliomas. A study of 243 patients was randomized to 5-ALA or none. Patients with complete resections survived an average of 16.7 months compared with 11.8 months in partial resection patients.[18] Stummer *et al*.[18] evaluated 143glioblastoma patients in a cohort study. The resection quality was determined with MRI at 72 h postoperatively. In patients with no residual disease, their median survival was longer than the follow-up period (24 months) and in patients with residual disease by MRI scan, their median survival was 13.9 months with >1.5 cm of residual disease.

Post-operative neurologic status has been shown to be predictive of survival, thus any surgical resection should be approached cautiously to preserve neurologic status. McGirt *et al*.[9] studied 306 patients with glioblastoma who underwent surgical resection. A total of 19 patients developed new motor deficits and 15 patients developed new language deficits postoperatively. Compared with patients who had no new deficits postoperatively, the 2-year survival rate decreased. A total of 23% of patients

with no deficits were alive at 2 years, compared with only 8% of patients with surgical motor deficits and none of the patients with postoperative language deficits.

Recurrent glioma resection has also been debated, with no real consensus on its usefulness at this time. There are many Class III studies showing promise for improved survival with re-resection.[5,14] Park *et al.*[11] published a study in 2010 evaluating 109 patients with recurrent GBMs. A scoring system was established for patients with recurrent tumors. One point is assigned for each of the following: Preoperative KPS score <80, tumor volume >50 cm3, and motor-speech-middle-cerebral artery score (MSM) score >2, which looks at involved eloquent areas. The score ranges from 0 to 3 and interestingly was shown to correlate with median survival post-operatively.

RADIATION THERAPY

The treatment of gliomas with RT remains controversial especially for low-grade tumors. Here, a large European prospective RCT evaluated the efficacy of RT for low-grade gliomas in patients from 1986 to 1997. Postoperative RT improved PFS but did not impact OS.[7,12] Others have also shown that early RT following surgery for low grade tumors improves PFS but does not affect OS when compared with delayed radiotherapy.[20]

A prospective randomized trial of low versus high dose RT in adults with supra-tentorial low-grade gliomas by Shaw *et al.*[16] demonstrated a lower survival and a higher incidence of radiation necrosis in the high radiation treatment group. Here the most important factors affecting prognosis of these patients was histologic sub-type, tumor size, and age.

For anaplastic oligodendrgoliomas (AO) and anaplastic oligoastrocytomas (AOA) the combination of chemotherapy and radiation did not significantly improve survival compared with radiation alone.[6] In fact the use of chemotherapy in this setting was associated with more toxicity. The study did, however, demonstrate that tumors lacking the 1p/19q deletion were less aggressive and more responsive to either therapy.

For high-grade tumors, the role of radiation is clearer. One of the most important studies to demonstrate this was the study assessing the impact of radiation alone versus radiation with concomitant TMZ in treating glioblastoma. The results demonstrated that radiation is safe and more efficacious when administered concomitantly with the chemotherapeutic agent TMZ.[19] Here, they found that the 2-year survival for the later was 26.5% compared with 10.4% for the radiation treatment group alone.

Overall, these results show that the role of RT in low-grade gliomas is less when defined and more studies need to be done to determine the appropriate time frame and chemotherapeutic combination necessary for improvements to OS. In high-grade gliomas, however, concomitant administration of RT and chemotherapy significantly improves OS of patients. Therefore, RT is key for improving overall patient survival with this devastating disease following surgery.

CONCLUSIONS

We have come a long way from the days of single modality approach to treating gliomas. Today, we work in multi-disciplinary teams on tumor boards to discuss treatments of patients because high level evidence suggests that a combination of different treatment modalities helps curb disease progression by limiting tumor burden, resistance and therefore recurrence. Lessons from clinical trials conducted over the past few decades suggests that response to various clinical agents varies across patients with the same histologically diagnosed tumor. With our knowledge of the genetic variability across histologically similar tumors in patients, we are now designing clinical trials and performing surgeries on patients not based on tissue diagnosis but on molecular information such as 1p19q deletion or MGMT hyper-methylation. Following more sub-type and molecular biology based clinical trials, we speculate that there will be use for some of the old agents that demonstrated no efficacy in large and heterogenous groups of patients. Ultimately, in the future, multi-modality glioma therapy will be personalized for individual patients based on tumor grade as well as histological and molecular sub-types.

REFERENCES

1. Deutsch M, Green SB, Strike TA, Burger PC, Robertson JT, Selker RG, *et al.* Results of a randomized trial comparing BCNU plus radiotherapy, streptozotocin plus radiotherapy, BCNU plus hyperfractionated radiotherapy, and BCNU following misonidazole plus radiotherapy in the postoperative treatment of malignant glioma. Int J Radiat Oncol Biol Phys 1989;16:1389-96.
2. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer 1993;71:2585-97.
3. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, *et al.* Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.
4. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, *et al.* A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
5. Helseth R, Helseth E, Johannesen TB, Langberg CW, Lote K, Ronning P, *et al.* Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. Acta Neurol Scand 2010;122:159-67.
6. Intergroup Radiation Therapy Oncology Group Trial 94021, Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, *et al.* Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 2006;24:2707-14.
7. Karim AB, Afra D, Cornu P, Bleehan N, Schraub S, De Witte O, *et al.* Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4:

An interim analysis. Int J Radiat Oncol Biol Phys 2002;52:316-24.
8. Levin VA, Silver P, Hannigan J, Wara WM, Gutin PH, Davis RL, *et al*. Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. Int J Radiat Oncol Biol Phys 1990;18:321-4.
9. McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attenello FJ, Olivi A, *et al*. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. J Neurosurg 2009;110:583-8.
10. Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, *et al*. Bevacizumab for recurrent malignant gliomas: Efficacy, toxicity, and patterns of recurrence. Neurology 2008;70:779-87.
11. Park JK, Hodges T, Arko L, Shen M, Dello Iacono D, McNabb A, *et al*. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol 2010;28:3838-43.
12. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, *et al*. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 2002;20:2076-84.
13. Prados MD, Scott C, Sandler H, Buckner JC, Phillips T, Schultz C, *et al*. A phase 3 randomized study of radiotherapy plus procarbazine, CCNU, and vincristine (PCV) with or without BUdR for the treatment of anaplastic astrocytoma: A preliminary report of RTOG 9404. Int J Radiat Oncol Biol Phys 1999;45:1109-15.
14. Rostomily RC, Spence AM, Duong D, McCormick K, Bland M, Berger MS. Multimodality management of recurrent adult malignant gliomas: Results of a phase II multiagent chemotherapy study and analysis of cytoreductive surgery. Neurosurgery 1994;35:378-88.
15. Shapiro WR, Green SB, Burger PC, Mahaley MS Jr, Selker RG, VanGilder JC, *et al*. Randomized trial of three chemotherapy regimens and two radiotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma. Brain Tumor Cooperative Group Trial 8001. J Neurosurg 1989;71:1-9.
16. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, *et al*. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002;20:2267-76.
17. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, *et al*. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: Results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys 1993;26:239-44.
18. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, *et al*. Extent of resection and survival in glioblastoma multiforme: Identification of and adjustment for bias. Neurosurgery 2008;62:564-76.
19. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
20. van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, *et al*. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial. Lancet 2005;366:985-90.
21. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Dowell JM, Reardon DA, Quinn JA, *et al*. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 2007;13:1253-9.
22. Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, *et al*. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg 1978;49:333-43.
23. Walker MD, Green SB, Byar DP, Alexander E Jr, Batzdorf U, Brooks WH, *et al*. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 1980;303:1323-9.
24. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, *et al*. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 2003;5:79-88.